

IN VIVO EXPERIMENTS USING SOLUBLE GUANYLYL CYCLASE BETA1 HIS 105 PHE MUTANT MICE: NO-VASODILATATION AND PENILE ERECTION FULLY DEPENDENT ON ACTIVATION OF SGC

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The nitric oxide/cyclic guanosine phosphate pathway plays a pivotal role in vasodilatation and as such also in penile erection. Because of its central role in this molecular pathway, sGC represents a very attractive and promising new target for the development of new treatments for hypertension and/or erectile dysfunction. The cloning of sGC from various species has revealed that the protein is a heterodimer composed of a larger α and a smaller β subunit, which are both required for catalysis. Although two α and two β isoforms have been characterised so far, only the sGC $\alpha_1\beta_1$ and the sGC $\alpha_2\beta_1$ isoforms have been shown to occur in vivo. To establish the functional role of sGC and its different isoforms in the mechanism of vasodilatation and penile erection we performed in vivo studies on β_1 His 105 Phe transgenic mice (sGC $\beta_1^{ki/ki}$ mice) and their littermates. Different agents were injected either intravenously or intracavernosally and the changes in mean arterial pressure (MAP) and intracavernosal pressure (ICP) were recorded in the anesthetized mice. Intravenous and intracavernosal injection of exogenous NO (SNP – Spermine/NO) resulted in a decrease of MAP and an increase in ICP respectively in the wild-type control mice. These responses are however completely abolished in sGC $\beta_1^{ki/ki}$ mice. Intravenous administration of L-NAME which induced an increase in MAP in sGC $\beta_1^{+/+}$ mice, had no effect when injected in sGC $\beta_1^{ki/ki}$ mice. Stimulation of the nervus cavernosus induced frequency-dependent increases in ICP in sGC $\beta_1^{+/+}$ mice but again no response could be observed in sGC $\beta_1^{ki/ki}$ mice. Responses to the sGC-independent agents forskolin and 8-pCPT-cGMP which were injected intracavernosally did not differ between the sGC $\beta_1^{ki/ki}$ mice and the sGC $\beta_1^{+/+}$ mice. These studies indicate that the NO-dependent vasodilatation and NO-dependent induction of penile erection is fully dependent on sGC. By comparing the results from this study with results obtained from a previous study using sGC $\alpha_1^{-/-}$ mice (where a remaining response could be observed to both exogenous and endogenous NO) we provide strong evidence for the contribution of the less abundantly expressed sGC $\alpha_2\beta_1$ isoform in the mechanism of vasodilatation and penile erection. The unaltered responses to sGC-independent agents confirm the specificity of the impaired sGC-related responses observed in sGC $\beta_1^{ki/ki}$ mice.